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ORIGINAL REPORT

# Studying co-medication patterns: the impact of definitions<sup>†</sup>

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## SUMMARY

**Purpose** To show the necessity of distinguishing several patterns of drug prescribing that may lead to co-medication. It is demonstrated how these different patterns can be investigated using large databases containing pharmacy data or reimbursement data.

**Methods** Two examples illustrate how the particular pattern of co-medication studied will influence the reported proportion of patients having co-medication, the use of antidepressants among people using anticonvulsants, and the use of antihistamines among people receiving penicillines.

**Results** Depending on definition and period considered, the percentage of anticonvulsant users co-medicated with antidepressants ranged from 5.8% (95%CI 5.0%, 6.8%) to 14.5% (95%CI 13.2%, 15.9%) in 2000. Comparing 2002 with 2000, the ratio of proportions ranged from 1.3 to 2.1. The percentage of people who received penicillines and were co-medicated with antihistamines ranged from 0.5% (95%CI 0.4%, 0.6%) to 9.7% (95%CI 9.3%, 10.2%) in 2000. Comparing 2002 with 2000, the ratio of proportions ranged from 1.2 to 1.6.

**Conclusion** The co-medication patterns investigated yielded clinical as well as statistically significant different estimates. The estimates differed up to a factor 2.5 for the drugs usually prescribed for long periods, and a factor 12 for drugs prescribed for short periods. Hence, we propose to distinguish the patterns 'co-prescribing', 'concomitant medication,' and 'possibly concurrent medication.' The research question determines the co-medication pattern of interest, and the drug and disease under study determine the time window. Copyright © 2006 John Wiley & Sons, Ltd.

**KEY WORDS** — co-medication; drug combinations; drug therapy; combination; polypharmacy; research methodology

**ABBREVIATIONS** — OED, Oxford English Dictionary (UK); NIH, National Institutes of Health (USA); Medline, An on-line library of bio-medical literature (USA); Embase, Excerpta Medica on-line Bibliographic Database (Europe); OTC, Over The Counter

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## INTRODUCTION

The use of two or more drugs is a general concern since efficacy and safety of most drugs are investigated for single use alone. In pharmacoepidemiology studies, the use of different drugs at the same time, has served as a proxy for severity of

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disease and as a proxy for co-morbidities. Also, co-medication has become an important concept in the context of prescribing quality markers.<sup>1</sup> A variety of terms is used to refer to the use of two or more drugs within the same time frame; co-medication, concomitant medication, concurrent medication, co-administration, and multiple pharmacotherapy. Medline and Embase thesauruses include 'drug combinations,' single preparations containing two or more drugs as a fixed dose, and 'drug therapy, combination,' two or more drugs administered separately for a combined effect, both terms implying intended use of two or more drugs together. Since no entry refers to the use of two drugs regardless of whether they are part of the same treatment, this variety of terms seems inevitable. This labyrinth of terminology causes problems because it hampers the replication and full appreciation of pharmacoepidemiology studies on a variety of issues as well as the search for knowledge on particular combinations of drug classes in daily clinical practice. It also complicates systematic reviews and meta-analyses. For example, in a review on concomitant psychotropic drug use in children and teenagers, definitions ranged from more than two psychotropic drugs being prescribed by the same doctor on the same day to the same patient to children who received within the same year prescriptions for two or more psychotropic drugs regardless of prescriber, which lead to a variety of poorly comparable estimates.<sup>2</sup> And a review on gender differences in the prescribing of antipsychotic drugs referred to patterns of co-medication with concurrent medication, adjunct drugs, concomitant drugs, and co-administered drugs without any explicit definition but implied the purposeful prescribing of two or more drugs to the same patient allowing for different prescribers.<sup>3</sup>

Consensus is called for to be able to communicate results unambiguously to clinicians and researchers. For the sake of clarity, let us define co-medication as the most general term that covers the actual taking of two prescription drugs on the same day, regardless of the prescribers' intentions. Then, since not all patterns of co-medication may be of equal interest and not all patterns lead to the same estimates of proportion of patients involved, several possible co-medication patterns ought to be distinguished. We aim to demonstrate the necessity of distinguishing several patterns of drug prescribing that may lead to co-medication, by illustrating the impact of different co-medication patterns on the proportion of patients having had co-medication in a large pharmacy database.

## METHODS

### *Definitions*

Several patterns of co-medication can be defined. In this paper three patterns are distinguished:

1. With the prefix 'co-' in the meaning of jointly,<sup>4</sup> 'co-prescribing' is defined as 'the jointly prescribing of more than one drug by the same prescriber on the same day.'
2. As concomitant means concurrent,<sup>4</sup> 'concomitant medication' is defined as the concurrent use of drugs as prescribed by one or more different medical doctors not necessarily on the same day. Co-prescribing and concomitant medication cover co-medication resulting from the use of drugs as intended by medical doctors.
3. Of course, co-medication may also result from two drugs simply being available to the patient because they have been dispensed within a certain time period and some left over pills may still be left in the medicine cabinet. This latter source of co-medication is classified as 'possibly concurrent.'

Co-prescribing as defined above would be suited to study the quality of prescribing, for example the prescribing of laxatives together with opioids. When one would study the prevalence of co-morbidities among users of any particular class of medication, the co-prescribing pattern would most likely result in an underestimation as patients who visit different medical doctors would not be counted as cases of co-medication. In this latter example, the concomitant pattern would be best suited. Now assume the scenario in which it is important for the pharmacist to detect all people who may take two drugs because new information just proved the combination to be potentially life threatening. In this scenario, the pharmacist would probably opt for the possibly concurrent co-medication pattern.

### *Definitions made operational*

Prescriptions were identified as co-prescribed if written by the same doctor on the same day to the same patient (Table 1). Concomitant medication was made operational as drugs dispensed within a certain time period while according to information available in the pharmacy computer system, the two prescriptions overlap in time. The duration of any prescription is derived by dividing the quantity dispensed by the daily dose prescribed as registered in the pharmacy.

Table 1. Classification of co-medication patterns

Pattern	Co-medication	Criteria		
		Same prescriber	Overlap	Time between prescriptions
Co-prescribing Concomitant	Intentional Likely	Y	Y	Same day
		—	Y	Same day
		—	Y	$\pm 7$ days
		—	Y	$\pm 15$ days
Possibly concurrent	Possibly	—	Y	$\pm 30$ days
		—	—	Same month
		—	—	Quartile
		—	—	Halve year
		—	—	Year

The following time windows were chosen; same day,  $\pm 7$  days,  $\pm 15$  days, and  $\pm 30$  days. Note that concomitant medication allows for different prescribers.

Operationally, concurrent medication is two or more drugs under study dispensed within a certain time period regardless of overlap between prescriptions. Hence, possibly concurrent medication is identical to (calendar) period of prevalence of a drug among the users of another drug. Periods investigated were month, quartile, halve a year, and year. Note that both ‘concomitant  $\pm 15$  days’ dispensed and ‘possibly concurrent–month prevalence’ have a similar study length of 30 or 31 days.

For example, Mr Smith received a prescription for an anticonvulsants refill from his neurologist that would last him 90 days when used according to doctors orders. When he collected antidepressants also prescribed by the neurologist the same day, this would be classified as co-prescribing. However, would he collect the antidepressants a week later, this would be classified as concomitant. Now, assume Mr Smith’s last anticonvulsants refill that would have lasted him 90 days, was 4 months before he entered the antidepressant prescription. This last pattern, would be a case of ‘possibly concurrent’ with a time window of halve a year or one full year, but not ‘possibly concurrent’ with a time window of same month or same quartile (see also Figure 1).

#### Data selection

As a source of pharmacy data The InterAction DataBase is used.<sup>5</sup> The InterAction DataBase is part of the collaboration between community pharmacists in the northern and eastern part of the Netherlands and the Department of Social Pharmacy, Pharmacoepidemiology and Pharmacotherapy at the University of

Groningen and comprises all prescriptions dispensed by community pharmacies regardless of reimbursement status, from 1994 up to now, and covers anonymized prescriptions for about 450 000 people since 1999.

As a first index drug anticonvulsants of the ATC category N03A entitled anticonvulsants were chosen.<sup>6</sup> As possible co-medication the drug group ‘antidepressants’ (ATC category N06A) was chosen, as this combination received a lot of attention lately, mainly in the context of the treatment of bipolar disorder.<sup>7,8</sup> Also, both drugs are usually intended for a longer period of treatment whereas the second example concerns drugs that are intended for a shorter period of use. The second index drug class was penicillines (ATC category J01C) with antihistamines (ATC category R06A) as co-medication. This combination was chosen because in contrast to the first example, both drugs are usually administered for short periods of time. In addition, in some instances the use of antihistamines may serve as a proxy for penicillines allergy.<sup>9</sup>

In the first example, the study group consisted of people between 5 and 54 years of age who received at least one anticonvulsant prescription in 2000. For members of the study group all prescriptions of anticonvulsants and antidepressants dispensed in the year 2000 were selected. To study concomitant medication with a time window of 1 month, antidepressant prescriptions dispensed in December 1999 and January 2001 were also selected. Similarly, a study group with prescriptions was retrieved for the year 2002. Since ‘the patient’ is the level of interest in the issue of co-medication, person is the unit of analysis. Thus all prescription data were aggregated at the person-level. In the second example, the study group consisted of people in the same age range who received at least one prescription for penicillines.

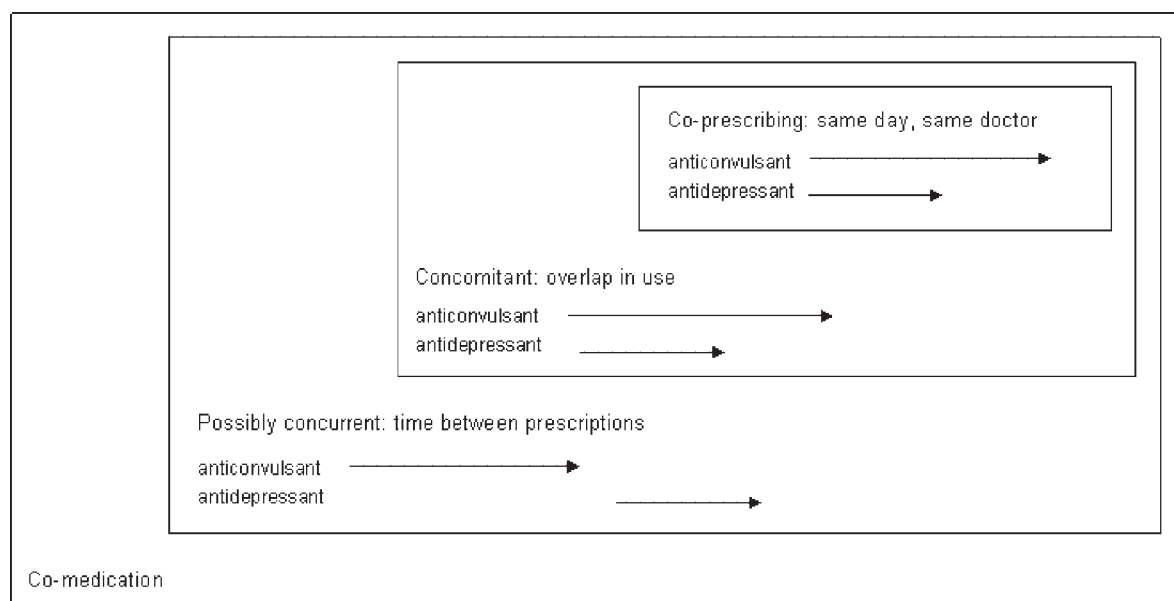


Figure 1. Co-prescribing, concomitant, and possibly concurrent medication: an example

Then, all prescriptions of penicillines and antihistamines for the members of this study group were selected as described above.

For all patterns of co-medication, the percentage of people with co-medication was calculated as the number of people who once or more fit the particular co-medication pattern divided by the number of people having received anticonvulsants (or penicillines) that same year. Ninety-five percent confidence intervals (CIs) were calculated using the 'Pearson-Clopper Exact method'.<sup>10</sup> To investigate the differences in trend for the co-medication patterns from 1 year to an other year, the ratio of the proportions for 2 years (the relative prevalence) was also calculated.

It should be noted that the different point estimates are not necessarily independent in the sense that the members of each study group contribute to the denominator of all point estimates in that example and contribute differently to the nominators. Since most of the statistical tests for the comparison of rates and proportions cannot handle this type of data structure, we used the crude method of confidence intervals not containing the other point estimate.

## RESULTS

In the year 2000, 2701 people had received at least one prescription for anticonvulsants. In 2002, a total of 2995 anticonvulsants people were dispensed. Depend-

ing on definition and period considered, the percentage of anticonvulsant users co-medicated with an antidepressant ranged from 6% to 14% in 2000. In 2002, these ranged from 10% to 18% (Table 2). The relative prevalence ( $\%2002/\%2000$ ) ranged from 1.2 to 1.9.

Table 3 shows the percentages of more than 27 000 people who received at least one prescription for penicillines and were co-medicated with antihistamines. The entries in this table are smaller than those in Table 2, reflecting the difference between drugs usually prescribed for a longer period versus ones prescribed for shorter courses. Depending on the definition and period considered, the percentage of penicilline users co-medicated with an antidepressant ranged from 0.5% to 9.7% in 2000. These percentages ranged from 0.9% to 11.2% in 2002. The relative prevalence ranged from 1.2 to 1.6.

In general, prevalence of co-medication increased with the time period considered. The difference between co-prescribing and concomitant same day could be clinically relevant but there is no statistical reason to differentiate between these two estimates in the presented examples (Tables 2 and 3). One would have expected the additional demand of overlap for classification as concomitant to result in smaller estimates than possibly concurrent. For the penicillines and antihistamines example, this expectation came true; concomitant  $\pm 15$  days and possibly

Table 2. Percentage of patients receiving anticonvulsants in 2000 ( $n = 2701$ ) and 2002 ( $n = 2995$ ) co-medicated with antidepressants according to the definitions and time windows described, and the ratio between the percentages in these 2 years

Pattern	Period	2000			2002			Ratio scale
		<i>n</i>	%	95% CI	<i>n</i>	%	95% CI	% 2002/% 2000
Co-prescribing	Same day	158	5.85	4.99, 6.80	312	10.42	9.35, 11.57	1.78
	Concomitant	166	6.15	5.27, 7.12	327	10.92	9.82, 12.09	1.78
Possibly concurrent	±7 days	179	6.63	5.72, 7.63	370	12.35	11.20, 13.59	1.86
	±15 days	216	8.00	7.00, 9.08	406	13.56	12.35, 14.83	1.70
	±30 days	267	9.89	8.79, 11.07	435	14.52	13.28, 15.84	1.47
	Month	226	8.37	7.35, 9.48	411	13.72	12.51, 15.00	1.64
	Quartile	282	10.44	9.31, 11.66	469	15.66	14.38, 17.01	1.50
	Half year	349	12.92	11.68, 14.24	503	16.79	15.47, 18.18	1.30
	Year	391	14.48	13.17, 15.86	531	17.73	16.38, 19.15	1.22
Total anticonvulsants users		2701	100.0		2995	100.0		

Table 3. Percentage of patients receiving penicillines in 2000 ( $n = 27\,149$ ) and 2002 ( $n = 27\,278$ ) co-medicated with antihistamines according to the definitions and time windows described, and the ratio between the percentages in these 2 years

Pattern	Period	2000			2002			Ratio scale
		<i>N</i>	%	95% CI	<i>n</i>	%	95% CI	% 2002/% 2000
Co-prescribing	Same day	143	0.53	0.44, 0.62	236	0.87	0.76, 0.98	1.64
	Concomitant	157	0.58	0.49, 0.68	260	0.95	0.84, 1.08	1.65
Possibly concurrent	±7 days	407	1.50	1.36, 1.65	606	2.22	2.05, 2.40	1.48
	±15 days	504	1.86	1.70, 2.02	750	2.75	2.56, 2.95	1.48
	±30 days	589	2.17	2.00, 2.35	870	3.19	2.98, 3.40	1.47
	Month	630	2.32	2.14, 2.51	938	3.44	3.23, 3.66	1.48
	Quartile	1137	4.19	3.95, 4.43	1616	5.92	5.65, 6.21	1.41
	Half year	1827	6.73	6.43, 7.03	2231	8.18	7.86, 8.51	1.22
	Year	2622	9.66	9.31, 10.2	3060	11.22	10.85, 11.60	1.16
Total penicilline users		27 149	100.0		27 278	100.0		

concurrent 1 month yielded statistically significant different estimates. However, this was not the case for the anticonvulsants and antidepressants; concomitant ±15 days and possibly concurrent 1 month yielded no statistically significant different results. The different patterns yield not only significant differences on the percentage scale but also on the ratio scale. All methods captured the trend in time, but the range in relative prevalence was considerable.

## DISCUSSION

Since co-medication is of general interest and the variety of terminology in use obstructs clear communication between clinicians and researchers, we proposed a first step towards unambiguous terminology by distinguishing three definitions. We illustrated

how these different definitions may lead to both clinically and statistically significant different proportions of people being co-medicated. The impact is also evident when looking at the relative prevalence of co-medication patterns, although all methods were able to capture the time trend.

We chose definitions and patterns in such a way that each of them is specially suited for different types of studies. We think of co-prescribing for the study of prescribing quality markers and severity of disease. Concomitant medication is suited for drug utilization studies into drug–drug combinations not investigated together for safety and efficacy and the study of co-morbidities. Possibly concurrent medication is most suitable when high sensitivity is demanded for, as is the case for the study of evident safety concerns. Clearly, the drugs of interest, the underlying ailments



being treated, the co-morbidities of interest, and possible safety aspects are important to consider when deciding on the time window.

This is not just a theoretical distinction without practical consequences as was shown in the two examples in this paper. For the percentage of people receiving anticonvulsants who were being co-medicated with antidepressants, the point estimates differed by a factor 2.5 (from 5.8% to 14.5%). The point estimates were smaller for the proportion of people receiving penicillines who were co-medicated with antihistamines, and these estimates differed by up to a factor 12. The relative prevalence (%2002/%2000) also showed a clinically significant range from 1.2 to 1.9 for the anticonvulsants with antidepressants, and 1.2 to 1.6 for the penicillines with antihistamines.

To our knowledge no previous study has investigated co-medication like the present study did, by means of examples of only hypothetical interest. Few studies went beyond the mere presenting of one proportion and these also showed large differences in point estimates of co-medication due to differences in time window. One study on pharmacotherapy among youths enrolled in Medicaid reported 13.6% of the children receiving at least two different classes of psychotropic drugs within a 1-week interval, and 42% of the children when a 3-month window was used instead.<sup>11</sup> A study on youths treated with stimulants that relied on pharmacy dispensing data, reported 15% of children being co-medicated with another psychotropic agent when using a 1-week interval and 21% when a 1-year prevalence was used.<sup>12</sup>

The completeness of medication dispensing data is essential for the study of co-medication patterns. The advantage of pharmacy dispensing data over claims data is that often all prescription medication is included regardless of reimbursement status of the particular drug. Pharmacy data will also be more complete on prescription medication than the GP's or specialist's files. However, in contrast to these, no information on switching medication is available in either pharmacy data or claims data. In addition, prescriptions not presented by the patient in the pharmacy may influence co-prescribing estimates derived from these databases. Especially in the study of co-medication with two drugs from the same class, this may be a problem as switching may be misclassified as co-medication and the other way around.<sup>13</sup>

According to Medline's thesaurus, co-medication means 'drug therapy, combination,' where two or more drugs administered separately for a combined

## KEY POINTS

- Co-medication is a term broadly and loosely used in clinical and epidemiology research.
- There is a labyrinth of terminology around 'co-medication' that hampers the replication and assessment of pharmacoepidemiology studies and the search for knowledge on particular combinations of drugs.
- Different co-medication patterns suited for different types of research questions, need to be distinguished.
- Different definitions of co-medication can lead to both clinically and statistically significant different proportions of people being co-medicated.
- It is both important and feasible to tailor the operational definition of co-medication to the research question at hand.

effect and demands the information on indication. Since reliable information on indication is available in neither pharmacy data nor claims data, 'drug therapy, combination' cannot be studied by depending on these data sources alone. However, these datasources are very suitable for the study of 'drug combinations,' meaning single preparations containing two or more active agents as a fixed dose (see Medline's thesaurus). It should be noted that Medline's thesaurus' entries are rather limited notions of co-medication since in pharmacoepidemiology co-medication is also used as a proxy for something that otherwise would be extremely hard to measure. For example, co-medication has been used as an indicator for prescribing quality,<sup>14</sup> severity of disease,<sup>15,16</sup> the presence of co-morbidity,<sup>17</sup> the prevalence of side effects,<sup>18</sup> and so on. So, whether or not our results are limited to pharmacy database research, they have huge consequences for research. Only after scrutinizing definitions and time-windows it is valid to make comparative statements like 'co-medication with antidepressants is less prevalent in the current study than in the literature' in drug utilization studies. Similarly, statements like 'The quality of prescribing has improved as inhaled bronchodilators are increasingly co-prescribed with inhalation corticosteroids' and 'The channeling of rofecoxib to patients who are co-medicated with a drug for the cardiovascular system suggests an overestimation of the cardiovascular risk of rofecoxib compared to other NSAIDs,'

can only be validly made when there is clarity about operational definitions.

In summary, by proposing three co-medication patterns and investigating these patterns empirically it was shown that it is both important and feasible to tailor the operational definition of co-medication to the research question at hand.

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